

REMARKS

The Office action

Claims 1-84 are pending. Claims 1-29 and 39-63 are withdrawn as being directed to nonelected subject matter. Claims 30-38 and 64-84 are rejected under 35 U.S.C. 112, first paragraph for lack of enablement. Claims 32, 75, 78, 79, and 81-83 are rejected under 35 U.S.C. 112, first paragraph as being indefinite. Claims 30-38, 65, 66-80, and 82-84 are rejected under 35 U.S.C. 102(e) as being anticipated by Weiss. Each of these rejections is addressed in turn.

Rejections under 35 U.S.C. 112, first paragraph

Claims 30-38 and 64-84 are rejected under 35 U.S.C. 112, first paragraph for lack of enablement. According to the Office, the specification does not enable the treatment of a patient having cell damage by administering the cells of the present invention. While applicants disagree with the position of the Office, applicants address this concern by amending the claims to recite a method of introducing cells of the invention; thus, the claims no longer require that a patient be treated by the introduced cells. Nor does the issue of immunologic rejection arise, as the amended claims do not require that the cells remain in the recipient for any extended period of time. Nevertheless, applicants direct the Office's attention to new claims 86 and 88, in which the cells that are introduced to the patient are from that patient, thus obviating any remaining concern the Office may

have about rejection.

Regarding claims 34 and 77, and the Office's concern about the lack of an established relationship between bacterial and viral infections and cell loss, applicants have cancelled these claims, and this basis for rejecting the claims may be withdrawn. Claims 37 and 79, drawn to methods of administering cells to a patient through the patient's bloodstream, have similarly been cancelled.

Rejections under 35 U.S.C. 112, second paragraph

Claims 32, 75, 78, 79, and 81-83 are rejected as being indefinite. Applicants have addressed these rejections by amendment, and the rejections may now be withdrawn.

Rejections under 35 U.S.C. 102(e)

Claims 30-38, 65, 66-80, and 82-84 are rejected as being anticipated by Weiss. According to the Office, the neural stem cells described by Weiss meet all of the limitations of these claims. The Office acknowledges that Weiss doesn't teach that these cells express fibronectin, but concludes that fibronectin expression "is an inherent property of the cells." To support this contention, the Office cites Campos et al. (Development 131:3433-3444, 2004), which, according to the Office, shows that "neural stem cells in neurospheres do express fibronectin." In fact, as is discussed below, the neural stem cells of Weiss do not express fibronectin.

Applicants have analyzed aggregates of applicants' stem cells as well as those of the neural stem cells of Weiss for expression of nestin and fibronectin. The two types of aggregates were processed identically, and the presence or absence of each molecule was determined by antibody labeling. The results of the analysis are shown in Exhibits A and B. In each case, the presence of nestin is indicated in green, and the presence of fibronectin is indicated in red. Fibronectin is an extracellular matrix (ECM) component that is localized on the cell surface. As is apparent in these exhibits, the skin-derived stem cells express fibronectin (Exhibit A), while the stem cells of Weiss do not (Exhibit B).

Applicants' results are not in conflict with those of Campos. Campos acknowledges that at the time the neurospheres are analyzed, some of the stem cells have differentiated and migrated to the center of the sphere (Campos, page 3437, left column). Thus, absent any more information, the fibronectin "diffusely localized in a speckled pattern" (Campos, page 3437, right column) could be produced by the stem cells or from the differentiate cells. Later, it becomes clear that it is the differentiated cells, and not the stem cells, that are expressing the fibronectin. At page 3442, left column, Campos states:

we have demonstrated a three dimensional architecture of neurospheres with cells expressing nestin and the EGF receptor, both molecules present in neural stem cells, being found at the outside edge of the sphere. Both laminin $\alpha 2$ and $\beta 1$ integrin are highly expressed by cells in this region, with other ECM molecules present within the sphere rather than around the edge.

In other words, laminin $\alpha 2$ and $\beta 1$ integrin are expressed in Campos's aggregates in a

manner that is coextensive with the expression of nestin—at the outer edge of the sphere.

Other ECM molecules—including fibronectin—are expressed within the sphere (where differentiated cells reside) and not at the outer edge (the location of the stem cells).

In sum, applicants have demonstrated that the stem cells described by Weiss do not express fibronectin, and that this conclusion is not in conflict with—and is indeed supported by—the findings of Campos.

As a final matter, applicants note that claim 69 has been amended to recite that the epithelial tissue is skin epithelium, while the cells of Weiss are derived from neuroepithelium. Thus, for this reason as well, claim 69 and claims dependent therefrom are not anticipated by Weiss.

Conclusion

Applicants note that the Form PTO 1449 that was submitted with an Information Disclosure Statement filed on December 4, 2002 has not been initialed and returned, and hereby request that it be initialed and returned with the next Office action.

Enclosed is a Petition to extend the period for replying to the Office action for three months, to and including April 15, 2005, and a check in payment of the required extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

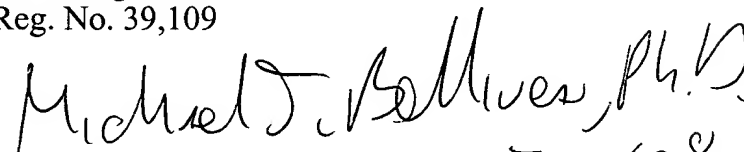
Date: _____

4/15/05



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EXHIBIT B

Immunolabeling of nestin (green) and
fibronectin (red) in cultured stem cells of Weiss

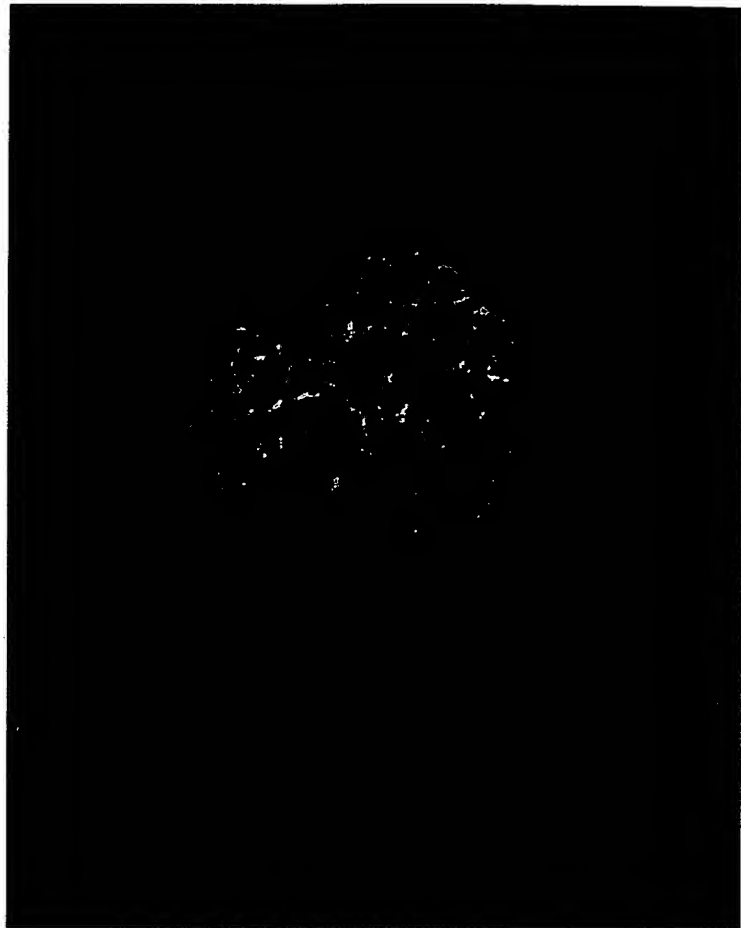




EXHIBIT A

Immunolabeling of nestin (green) and
fibronectin (red) in cultured SKPs

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